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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
MEAH, MOHAMMAD Y

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/650,591	AFEYAN ET AL.	
	Examiner	Art Unit	
	Mohammad Meah	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2007*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *Claims 1, 3-5, 14-34 and 37-41,* is/are pending in the application.

4a) Of the above claim(s) *3,28 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,14-34 and 37-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____is/ are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 10/26/07 has been entered.

With supplemental amendment of this application, the applicants, on 10/25/ 2007 cancelled claims 35 and 36. Claims 3, 28-29 remain withdrawn. Claims 1, 3-5, 14-34 and 37-41 are pending.

Applicants arguments for withdrawal of the finality of the prior office action are found to be persuasive and therefore prior office action is considered as non-final.

Claim Rejections

35 U.S.C 112

35 USC 112 2nd paragraph

Rejection of claim 16 under USC 112 *2nd paragraph* requirement is withdrawn after amendment of the claim by the examiner.

35 U.S.C 112

Enablement requirement

Claims 38-40 remain rejected under 35USC enablement requirement.

Claims 38-40 recite an adzyme composition formulated in any way to present autocatalytic proteolysis (38) or wherein specifically a reversible inhibitor is added (39-40). As explained in prior action and restated again, however reversible inhibitors are not likely available for many protease and other means of formulating to inhibit autocatalysis are not taught. Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any substrate and their by-product. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of substances having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Applicants arguments, on pages 6-8 of their amendment against rejection of claims 38-40 under 35 U.S.C 112, first paragraph enablement requirement are acknowledged. Applicants' arguments against rejection of claims 38-40 is not found persuasive as explained in prior action because these claims are directed to an adzyme wherein **any** substrate polypeptide is cleaved by said adzyme to produce any product that inhibits the substrate binding or adzyme cleavage. Therefore, as explained in the previous office action and explained above again the specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, make and for use the invention commensurate in scope with these claims.

Applicants argue that the claimed inventions are enabled because it is well known in the art many molecules, such as cytokine, after proteolytic cleavage, inhibit the binding of the receptor. However the recitation in the claims include broad class of molecules not only cytokines and even within cytokines this is true only for specific cleavages of specific cytokines. Not all cleavage products of all cytokines and cytokine receptors antagonize the action of the receptor. Many would simply eliminate activity (in fact most cleavage probably have these effect) and a few would not alter activity at all. Applicant suggested said explanation to other class of signaling molecules however as different signaling molecules bind or inhibit using different structural and functional moieties than that of cytokines, same argument may/or may not applies. Applicant assert that with the knowledge of structure and function of the prior art cytokines and the knowledge of applicant adzyme which catalyses proteolytic cleavage of cytokine type of polypeptide, skilled artisan is enabled to identify **any** substrate polypeptide, which is cleaved by adzyme to produce any product that inhibits the substrate binding or adzyme cleavage. It is not found persuasive because the disclosure of one or more particular instances of a particular cleavage which produces a product which acts as an antagonist is no way provides guidance for finding suitable cleavages of all cytokines much less of any substrate polypeptide. Similarly reversible inhibitors are not likely available for many proteases and recited protease inhibitors in page 10 of applicants arguments may or may not bind reversibly with any particular protease to inhibit autocatalysis. While enablement is not precluded by the necessity for routine screening, if a large amount of

screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification.

CLAIM Rejection - 35 U.S.C 102

Rejection of Claims 1, 4, 14, 16-25, 30-40 are rejected under 35 U.S.C. 102(e) as being anticipated by Chen et al. (US 2003/0068792) is withdrawn. Applicants argument against Chen et al. (US 2003/0068792),, is found persuasive mainly because although Chan does tech fusion protein but however does not specific fusion protein wherein catalytic domain and targeting domain are discrete and heterologous with respect to each other. therefore rejection based on Chen et al is withdrawn.

The 102 rejections of claims 1, 4, 14, 16-25, 30-41 under 35 U.S.C. 102 Davis et al. (WO 00/64485) of the previous office action are still remained applicable.

Claims 1, 4, 14, 16-26, 30-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Davis et al. (WO 00/64485) as explained by the previous office action.

Applicants argument that Davis et al do not teach a fusion protein is not found persuasive because, like applicants (applicants claim 14-15), Davis et al.

fuse a catalytic domain (like protease) to a targeting moiety via chemical cross linking agent. Moreover applicants arguments that Davis "teach away" from fusion proteins is not true, on the contrary Davis et al teach a fusion protein comprising catalytic domain with a targeting domain. Like applicant's fusion of catalytic domain to targeting domain, Davis et al teach cross linking catalytic domain with targeting domain. Fusion of two or more proteins or polypeptides via chemically or recombinantly form a "fusion protein". Therefore Davis et al. teach " fusion protein."

CLAIM Rejection - 35 U.S.C 103a

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4 14-17, 18 19-21, 22-27, 30 -38, 41 are rejected under 35 U.S.C. 103(a) by Davis et al. (WO 00/64485) , Guo et al. (Biotec and Biong 2000, 70, 456-463) in view of Sallberg et al. (US 6960569) or whitcomb et al. (US PAT 6406846).

Davis et al. teach fusion proteins wherein enzymes (serine protease, chymotrypsin, etc) which catalyse degradation of a specific target are conjugated to binding partners wherein the binding partner is an antibody (immunoglobulin) **to the**

target with or without a linker and resulting fusion protein has greater (catalytic or more than one) activity than the unconjugated molecule. The chimeric protein of Davis et al. bind to the target and the antagonize/inhibit/degrade a wide variety of receptors and/or intermediary signaling molecules such as cytokines, EGF-like factors, etc. Davis et al. use the fusion protein as a pharmaceutical composition wherein the targeted enzyme is protease and use the pharmaceutical composition for autoimmune disease, infectious diseases , cancer, etc.

Guo et al. teach fusion proteins wherein enzyme (ASNase) conjugated to immunoglobulin or fragment or antibody (scFV) by a linker polypeptide $(Gly_4Ser)_3$.

Whitcomb et al. (US PAT4510251) teach mesotrypsin – a trypsin-like protease (page 10 1st paragraph) that is resistant to trypsin inhibitor and also teach that mesotrypsin rapidly degrades and inactivate zymogens and other polypeptides. Most trypsin type protease is inhibited by PSTI whereas mesotrypsin is resistant to PSTI inhibitor). Therefore there is a **motivation** to make a fusion protein wherein the protease domain is mesotrypsin.

Sallberg et al. (US 6960569) teach fusion protein of mutated NS3/4A protease domain of HCV conjugated to antibody or other protein wherein fusion protein is resistant to proteolytic cleavage (mutation of breaking point residues of protease causes resistance to the proteolitic cleavage)

As such it would have been obvious to one of ordinary skill in the art to use mesotrypsin – a trypsin-like protease that is resistant to trypsin inhibitor as taught by

Whitcomb et al. or mutation of protease as taught by Sallberg and conjugate said proteases by a linker as taught by Guo et al. to targeting domain as thought by Davis et al. (WO 00/64485) and use the resulting adzyme to inactivate substrate polypeptides by catalyzing the proteolytic cleavage of the said substrate polypeptide.

Applicants argument against combining Davis et al. and Whitcomb et al is not found persuasive because Whitcomb et al teach a mesotrypsin system wherein mesotrypsin is resistant to pancreatic secretory trypsin inhibitor (PSTI). PSTI inactivate protease. Therefore one knowledgeable in prior art is **motivated** to use mesotrypsin in stead of other type of protease (such as serine protease) as a catalytic domain since in in-vivo application, as taught by Davis, compared to other proteases (as PSTI will inactivate them), mesotrypsin will remain active.

Applicants argument against combining Chen et al., is found persuasive is withdrawn.

However combining Davis et al with Whitcomb et al. (US PAT4510251) is not found persuasive because as explained above Davis et al teach fusion protein wherein a protease domain is fused with a variety of targeting domain comprising antibody, polypeptide, etc so that the fusion protein bind to the substrate and the antagonize/inhibit/ degrade a wide variety of substrate and/or intermediary signaling molecules such as cytokines, EGF-like factors, etc. Aapplicants argument that Davis et al do not teach a fusion protein is not found persuasive because, like applicants (applicants claim 14-15), Davis et al. fuse a catalytic domain (like protease) to a targeting moiety via chemical cross linking agent. About the argument against resistant to auto cleavage prior action adequately explained that active protease inherently some extent resistant to auto

cleavage (see argument in 102 rejection for which applicant did not argue): illustrated again:

"Applicant's argument, that Davis et al. (WO 00/64485), does not teach fusion proteins that are resistant to autoproteolytic cleavage is not found to be persuasive because although the cited references did not mention the resistivity to auto proteolysis, there is no available evidence to suggest that they are labile to autoproteolysis and furthermore as their fusion proteins are stable enough to show protease activity to cleave substrate polypeptide they must inherently be resistant to self cleavage."

Applicants augment that Sallburg et al. does not teach that their NS3/4A is not resistant to auto cleavage is not found to be true because as shown (paragraph 11) in the their specification NS3/4A mutant lack proteolytic site and therefore lack proteolysis cleaving properties.

Double Patenting Rejection

Examiner agrees with applicant that provisional Double patenting rejection will be withdrawn upon allowance when applicant submit terminal disclaimer.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Examiner, Art Unit 1652

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